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2017-08-30

Huhtaniska , S , Jaaskelainen , E , Heikka , T , Moilanen , J S , Lehtiniemi , H , Tohka , J , Manjon , J V , Coupe , P , Bjornholm , L , Koponen , H , Veijola , J , Isohanni , M , Kiviniemi , V , Murray , G K & Miettunen , J 2017 , ' Long-term antipsychotic and benzodiazepine use. and brain volume changes in schizophrenia : The Northern Finland Birth Cohort 1966 study ' , Psychiatry Research. Neuroimaging , vol. 266 , pp. 73-82 . https://doi.org/10.1016/j.pscychresns.2017.05.009

http://hdl.handle.net/10138/298050
https://doi.org/10.1016/j.pscychresns.2017.05.009

publishedVersion

Psychiatry Research: Neuroimaging 266 (2017) 73–82

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

# Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study

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ARTICLE INFO

*Keywords:*
Schizophrenia
Antipsychotics
Benzodiazepines
Brain
MRI

ABSTRACT

High doses of antipsychotics have been associated with loss in cortical and total gray matter in schizophrenia. However, previous imaging studies have not taken benzodiazepine use into account, in spite of evidence suggesting adverse effects such as cognitive impairment and increased mortality. In this Northern Finland Birth Cohort 1966 study, 69 controls and 38 individuals with schizophrenia underwent brain MRI at the ages of 34 and 43 years. At baseline, the average illness duration was over 10 years. Brain structures were delineated using an automated volumetry system, volBrain, and medication data on cumulative antipsychotic and benzodiazepine doses were collected using medical records and interviews. We used linear regression with intracranial volume and sex as covariates; illness severity was also taken into account. Though both medication doses associated to volumetric changes in subcortical structures, after adjusting for each other and the average PANSS total score, higher scan-interval antipsychotic dose associated only to volume increase in lateral ventricles and higher benzodiazepine dose associated with volume decrease in the caudate nucleus. To our knowledge, there are no previous studies reporting associations between benzodiazepine dose and brain structural changes. Further studies should focus on how these observations correspond to cognition and functioning.

## 1. Introduction

Progressive changes in the brain structures of individuals with schizophrenia compared to healthy controls have been reported especially in frontal and temporal lobes, anterior cingulate, hippocampus, amygdala, thalamus and insula (Shepherd et al., 2012; Torres et al., 2013). The possible effects of antipsychotics on brain structure and functioning have been of intensive study in recent years (Andreasen et al., 2013; Ho et al., 2011; Radua et al., 2012), and a meta-review concluded that previous comparisons between healthy controls and people with schizophrenia may be, at least partly, confounded by the effects of medication (Shepherd et al., 2012). However, in spite of several reviews and meta-analyses (Fusar-Poli et al., 2013; Roiz-Santiáñez et al., 2015; Vita et al., 2015) on the association between antipsychotics and brain volume changes, the results are inconclusive with a need for further studies.

Many imaging studies in schizophrenia are conducted in the early phase of the illness, mostly during the first episode, when the possible

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http://dx.doi.org/10.1016/j.pscychresns.2017.05.009
Received 15 December 2016; Received in revised form 12 May 2017; Accepted 19 May 2017
Available online 20 May 2017
0925-4927/ 

long-term effects of medications may not yet be noticeable. However, studies in rodents suggest that the effects of antipsychotics on the brain are evident also at later stages of the treatment (Terry et al., 2008, 2007a, 2007b; Terry and Mahadik, 2007). Some studies focus on patients drawn from clinics serving chronic patients, where the patients might be on average sicker and therefore not representative of the great variety of different stages of illness found in entire population suffering from the disease. Clinical trials with strictly defined medication doses over years of follow-up are hard to conduct, and few include imaging measures in their protocol. Therefore the data from naturalistic settings are crucial when examining potential long-term effects and adverse effects of antipsychotic treatment (Wang et al., 2011).

Pharmacological treatment of schizophrenia is not limited to antipsychotic medication. Benzodiazepines are commonly used in schizophrenia as sedatives or anxiolytics and to reduce aggressiveness and ease agitation. In schizophrenia, benzodiazepine use has been associated with increased risk of mortality even after controlling for potential confounders (Fontanella et al., 2016) and, in general, benzodiazepine use has been associated with not only increased mortality (Tiihonen et al., 2016) but also cognitive impairment (Baandrup et al., 2017; Barker et al., 2005, 2004a, 2004b). Although the mechanism of these effects is unknown, adverse effects on brain health such as accelerated ageing (Koutsouleris et al., 2014; Schnack et al., 2016), or individually varying decreases in brain volume (Schnack et al., 2016), are possible candidate mechanisms that merit investigation. In the general population, approximately 3% use benzodiazepines over 6 months, which is defined as long-term treatment (Kurko et al., 2015). Recently chronic benzodiazepine use has been associated with decrease in brain plasticity in mice (Curto et al., 2016), but there are no modern structural imaging studies on benzodiazepine effects on the human brain. Previous studies have used computed tomography (CT) to study the effect of benzodiazepine use mainly on ventricular enlargement (Busto et al., 2000; Lader et al., 1984; Moodley et al., 1993; Perera et al., 1987; Schmauss and Krieg, 1987; Uhde and Kellner, 1987), but to our knowledge there are no previous MRI studies on benzodiazepine effects on brain structures in schizophrenia (or other conditions).

Because antipsychotic medication is the key treatment in schizophrenia and other psychoses, it is highly important to take possible confounding factors into account when studying potentially harmful effects of antipsychotic medications. Important confounding factors are for example illness duration and severity, age, sex, and other long-term medications. Nevertheless, only a few previous studies on long-term follow-ups have taken into account illness severity measures when analyzing antipsychotic effects on brain structures (Huhtaniska et al., 2017).

In this study our aim was to analyze, in a population-based sample of schizophrenia cases with illness duration on average of 10 years at baseline, whether a nine-year scan-interval antipsychotic or benzodiazepine dose would have an effect on brain structural changes. This is the first longitudinal MRI study that we are aware of to investigate the effects of benzodiazepines on brain structure in schizophrenia and to examine the effects of antipsychotic medication on brain structure in schizophrenia whilst controlling for benzodiazepine use.

## 2. Methods

### 2.1. Study sample

This study is based on an unselected, general population birth cohort called The Northern Finland Birth Cohort 1966 (NFBC1966). The Ethical Committee of the Northern Ostrobothnia Hospital District has approved the NFBC1966 project and keeps its study design under continuous review. The sample collection is described in more detail in our previous publications using a partly overlapping sample (Guo et al., 2015; Veijola et al., 2014) and in the Supplementary Methods.

Forty-five individuals with schizophrenia spectrum disorder and 77 non-psychotic controls participated in both baseline and follow-up studies when the participants were approximately 34 and 43 years old. At baseline the diagnoses were validated (Isohanni et al., 1997; Moilanen et al., 2003) using the Structured Clinical Interview for DSM-III-R (SCID-I; Spitzer et al., 1989) criteria and anamnestic information including individual hospital medical records. The original diagnoses were confirmed at the follow-up using Structured Diagnostic Interview for DSM-IV (First et al., 2002) and information from medical records. SCID-I was also completed for controls at both time points.

For seven participants with schizophrenia spectrum disorder and seven controls MRI data were incomplete (scans missing or too poor quality at either time-point). One of the controls had a psychotic episode during the follow-up period according to the Care Register for Health Care (CRHC) and was not included in the final study group. Therefore, the final schizophrenia spectrum group included 38 participants and the control group 69 participants. The specific diagnoses for the schizophrenia spectrum group were schizophrenia ($n = 33$), schizophreniform disorder ($n = 1$), schizoaffective disorder ($n = 3$) and delusional disorder ($n = 1$). Hereafter the term schizophrenia is used to refer to schizophrenia and other schizophrenia spectrum disorders. The sample collection is described in more detail in Supplement Fig. 1 and in Supplementary Methods.

In schizophrenia group the participants did not differ statistically significantly from the non-participants and are representative of the entire schizophrenia population in NFBC1966 regarding age, sex and educational level. In the control group, the participants' level of education was higher than of the non-participants (Veijola et al., 2014).

### 2.2. Data on medication

Lifetime psychiatric medication use was collected using all available medical records (hospital and out-patient care case notes), an interview conducted at both baseline and follow-up, and the register of the Finnish Social Insurance Institution on psychoactive medications consumed during 1997 (Husa et al., 2014; Veijola et al., 2014). The medical records were acquired on the basis of information concerning the subjects' treatment facilities, which we received from the CRHC. If the subject had no information in the CRHC, we requested medical records from the outpatient facilities of the subjects' area of residence. Participants in this study had given their permission to collect medical records by signing the written informed consent. We had permission for collecting the data from the Ministry of Social Affairs and Health.

All medical records were reviewed to record the name of the drug, dose and time period the medication had been used. Drugs were categorized by using the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2010). Antipsychotics included classes N05A (antipsychotics) and Pertriptyl (N06CA01 combination medicine including perphenazine). Benzodiazepines included ATC classes N05BA (anxiolytics, benzodiazepine derivatives), N05CD (hypnotics and sedatives, benzodiazepine derivatives), and N05CF (hypnotics and sedatives, benzodiazepine-related drugs). For antipsychotic medication, the information was used to calculate the cumulative doses of lifetime and interscan interval antipsychotic doses expressed as dose-years of a daily dose of 100 mg chlorpromazine (CPZy) using several sources, see Moilanen et al. (2015) for details. For benzodiazepines, the information was used to calculate the defined daily doses (DDD) (Nykänen et al., 2016; Rissanen et al., 2015) and these were then expressed as benzodiazepine dose-years (BZDy). One BZDy is equivalent to the amount of benzodiazepine medication, which a person would use if the daily dose was 1 DDD and the duration of treatment would be one year. All the used medications are listed in Supplement Table 1.

### 2.3. Covariates and background variables

Onset age of the illness was ascertained from medical records and it was defined as the age of first evident psychotic symptoms. Clinical

symptoms in participants with schizophrenia at baseline and follow-up were examined using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). In the baseline study, the PANSS was measured based on the SCID I -interview and general psychiatric interview, while in the follow-up study PANSS was defined using a specific PANSS interview. The number of hospital days during the follow-up was collected from the CRHC. We used hospital treatment days as an additional measure of illness severity, because it is the only available variable that reflects the illness severity status over the entire follow-up period. Remission was assessed using the Andreasen criteria (Andreasen et al., 2005), but the symptoms were only required not to be present during the period of one week before the assessment, and no duration criteria was used since PANSS was done only once at baseline and follow-up. At follow-up, we gathered information on medication related side-effects, such as extrapyramidal symptoms or weight gain, using the LUNSERS scale (Day et al., 1995).

### 2.4. MRI methods

The participants were scanned with the same 1.5 T GE Signa scanner (General Electric, Milwaukee, Wisconsin) at both baseline and follow-up at the Oulu University Hospital. At baseline T1-weighted high-resolution three dimensional spoiled gradient echo (3D SPGR) images were acquired in the coronal plane covering the whole brain (slice thickness 1.5 mm; in-plane resolution matrix size 256 × 256; voxel size 1.5 mm × 1 mm × 1 mm; repetition time 35 ms; echo time 5 ms; flip angle = 35). Prior to the follow-up imaging the scanner was up-graded into HDxt with a new gradient system and parallel image data acquisition with an 8 channel receiving coil. At follow-up, the T1 weighted images were acquired with a 3D fast spoiled gradient echo (FSPGR) sequence (slice thickness = 1 mm; in-plane resolution matrix size 256 × 256; voxel size 1 $mm^3$; repetition time 12.576 ms; echo time 5.3 ms; flip angle = 20).

### 2.5. MRI data processing

To extract the brain tissue volumes from the MRI images we used an online automated MRI brain volumetry system volBrain (http://volbrain.upv.es/) (Manjón and Coupé, 2016). VolBrain segments the MRI into 15 different brain tissue classes or structures (white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), brain (WM + GM), intracranial cavity, cerebrum, cerebellum, brainstem, lateral ventricles, caudate, putamen, thalamus, globus pallidus, hippocampus, amygdala, accumbens) separated in right and left if applicable. Details on the image processing pipeline are provided in Supplementary Methods. In this study we focused mainly on subcortical structures.

Since there are many concerns regarding the methodology and replicability of measures in longitudinal MRI studies, and as we had a scanner update during the follow-up, we performed a calibration scan inviting 15 controls to be scanned with both used protocols during the same day to assess the possible effect of the scanner update on our measurements. With the help of these calibration-scans, we measured the inter-scan reliability rates for each extracted brain structure volume and excluded the structures with single measures intraclass correlation poorer than 0.90. For more information on the calibration scan and reliability measures, see Supplementary Methods and Supplement Table 2.

We calculated the annual change of each studied brain region using the total change during the follow-up and the length of follow-up for each individual.

### 2.6. Statistical analyses

The brain structural MRI changes were examined in 10 different measures based on the interest in subcortical structures and our inter-scan reliability measures. These areas were: total brain, total gray matter (GM), cerebrum, cerebral GM, lateral ventricles, caudate nucleus, putamen, thalamus, hippocampus, and nucleus accumbens. We analyzed differences between subjects with schizophrenia and non-psychotic controls and associations between medication doses during the scan interval and brain areas in the schizophrenia group. We applied a logarithmic transformation to medication data and the number of hospital days during the follow-up due to skewness of these variables and used them as continuous variables in analyses.

All analyses were made by linear regression with sex and baseline ICV as covariates. In medication analyses, we added the average PANSS score between the two time points and hospital treatment days during the follow-up as additional covariates. We also added benzodiazepine BZDy as a covariate in analyses of CPZy, and vice versa.

As post hoc analyses we divided the schizophrenia group in to 4 subgroups based on median doses of antipsychotics and benzodiazepines and looked at the subgroup findings in areas that were statistically significant in the original analyses. Based on the antipsychotic/benzodiazepine medication dose, the 4 subgroups were high/high ($n$ = 12), high/low ($n$ = 7), low/high ($n$ = 6) and low/low ($n$ = 13). We tested whether there would be an interaction between antipsychotic and benzodiazepine status (high/low) in the brain areas with statistically significant findings. We also did additional analyses to see whether alcohol use disorder diagnosis would affect the brain structural changes in the schizophrenia group.

The analyses were performed using IBM SPSS Statistics version 23 using $p < 0.05$ as a limit for statistical significance.

## 3. Results

### 3.1. Characteristics of the sample

The characteristics of the schizophrenia group are described in Table 1. In schizophrenia group the number of males was 21 (54%), age at baseline was on average 33.7 years and the length of follow-up was 9.1 years. At baseline 13 (34%) subjects were in remission and at follow-up 12 (32%). Fourteen (37%) subjects were on disability pension at baseline and the average PANSS score between the two time points was 61.4 (SD 20.7).

Schizophrenia cases showed statistically significant decreases in the volumes of total brain ($t = -2.27$, $p = 0.025$), cerebrum ($t = -0.38$, $p = 0.019$), caudate nucleus ($t = -4.05$, $p < 0.0001$), thalamus ($t = -0.14$, $p = 0.035$) and hippocampus ($t = -0.023$, $p = 0.028$) when compared to controls. All results on case control differences are presented in Supplement Table 3 and the average volume change in cases and controls is presented in Supplement Table 4.

### 3.2. Medication use characteristics

Medication use characteristics of the schizophrenia group are described in Table 2. Before baseline 37 (97%) schizophrenia subjects had been medicated with antipsychotics. All of them had used typical antipsychotics and 20 (53%) had used atypical antipsychotics. The mean cumulative dose of antipsychotics by baseline was 27.6 (SD 34.9) CPZy.

During the follow-up 34 (90%) subjects used antipsychotics. Five subjects (13%) used only typical antipsychotics and six subjects (15%) used only atypical antipsychotics. Twenty-three (61%) subjects used both typical and atypical antipsychotics during the follow-up. The mean dose of antipsychotics during the follow-up for all medicated subjects was 28.5 (SD 24.8) CPZy, for subjects using only typical antipsychotics 7.7 (SD 9.3) CPZy, and for subjects using only atypical antipsychotics 19.0 (SD 18.7) CPZy.

Before baseline 36 (95%) subjects had used benzodiazepines. Five (14%) subjects had used benzodiazepines only irregularly (prescribed to be taken only when needed). The mean cumulative dose of benzodiazepines by baseline was 3.6 (SD 4.3) BZDy. During the follow-up 30 (79%) subjects used benzodiazepines. Ten (33%) subjects used

**Table 1**
Characteristics of the schizophrenia group (N = 38).

| | N | % |
|---|---|---|
| **Gender Male/Female** | 21/17 | 55.3/44.7 |
| **Educational level at baseline** | | |
| Basic (< 9 years) | 20 | 52.6 |
| Secondary (9–12 years) | 9 | 23.7 |
| Tertiary (> 12 years) | 9 | 23.7 |
| **Marital status at baseline** | | |
| Married/cohabited | 11 | 28.9 |
| Not married/cohabited | 27 | 71.1 |
| **Working status at baseline** | | |
| Disability pension | 14 | 36.8 |
| Employed | 14 | 36.8 |
| Other (unemployed, not in working life due to other reasons than disability pension) | 10 | 25.6 |
| **Comorbid diagnose of alcohol use disorder at baseline** | | |
| No /Yes | 29 / 9 | 76.3 / 23.7 |
| **Number of patients hospitalized before baseline** | 37 | 97.4 |
| **Remission at baseline/follow-up** | 13/12 | 34.2/31.6 |
| **Extrapyramidal symptoms at follow-up** | 5 | 13.2 |
| **Weight gain due to medication** | 3 | 7.9 |
| **Clozapine use during the follow up** | 7 | 18.4 |
| **Diagnosis** | | |
| Schizophrenia | 33 | 86.8 |
| Undifferentiated type | 18 | 54.5[a] |
| Paranoid type | 6 | 18.2[a] |
| Disorganized type | 7 | 21.2[a] |
| Residual type | 2 | 6.0[a] |
| Schizophreniform disorder | 1 | 2.6 |
| Schizoaffective disorder | 3 | 7.9 |
| Delusional disorder | 1 | 2.6 |
| | **Mean (SD)** | **Range** |
| **Age of onset (years)** | 23.1 (4.4) | 16.7–31.0 |
| **Age at baseline (years)** | 33.7 (0.7) | 32.6–35.4 |
| **Age at follow-up (years)** | 42.8 (0.5) | 41.8–44.0 |
| **Follow-up length (years)** | 9.1 (0.6) | 7.5–10.2 |
| **Duration of illness (years) at baseline/ follow-up** | 10.6 (4.4)/ 19.7 (4.5) | 2.8–18.6/ 11.9–26.8 |
| **Average total PANSS score** | 61.4 (20.7) | 30–95 |
| **Number of hospital treatment days until baseline** | 514.4 (892.6) | 0–4703 |
| **Number of hospital treatment days during the follow-up** | 86.3 (129.1) | 0–594 |
| **Number of hospital treatment days in hospitalized patients during the follow-up** | 131.1 (139.9) | 2–594 |

[a] Of the 33 schizophrenia cases.

**Table 2**
Medication use characteristics of schizophrenia cases (N = 38).

| | N (%) | Mean dose (Median) | IQR |
|---|---|---|---|
| **Use of antipsychotics before baseline in CPZy** | | | |
| Use of antipsychotics | 37 (97.4) | 27.6 (14.0) | 4.6–44.3 |
| Use of typical antipsychotics | 37 (97.4) | 21.6 (8.7) | 2.6–30.4 |
| Use of atypical antipsychotics | 20 (52.6) | 11.0 (5.9) | 1.6–11.0 |
| Use of clozapine | 9 (23.7) | 16.7 (9.8) | 1.6–29.8 |
| **Use of antipsychotics during the follow-up in CPZy** | | | |
| Use of antipsychotics | 34 (89.5) | 28.5 (20.8) | 8.8–43.7 |
| Use of typical antipsychotics | 28 (73.7) | 9.4 (6.1) | 0.5–14.3 |
| Use of atypical antipsychotics | 29 (76.3) | 24.3 (20.3) | 6.4–38.7 |
| Using typical antipsychotics only | 5 (13.2) | 7.7 (4.5) | 0.1–16.8 |
| Using atypical antipsychotics only | 6 (15.8) | 19.0 (12.5) | 4.3–37.7 |
| Using both typical and atypical antipsychotics | 23 (60.5) | 35.5 (38.2) | 11.6–48.9 |
| Use of clozapine | 7 (18.4) | 3.2 (3.6) | 2.0–3.8 |
| **Use of benzodiazepines in BZDy** | | | |
| Use of benzodiazepines before baseline scan | 36 (94.7) | 3.6 (2.5) | 0.3–4.8 |
| Use of benzodiazepines only irregularly before baseline scan | 5 (13.8) | 1.1 (0.6) | 0.3–2.2 |
| Use of benzodiazepines during the follow-up | 30 (78.9) | 4.1 (3.3) | 0.8–5.1 |
| Use of benzodiazepines only irregularly during the follow-up | 10 (33.3) | 1.6 (1.1) | 0.7–3.3 |
| **Use of both antipsychotics and benzodiazepines during the follow-up** | 30 (78.9) | 4.1 (3.3) BZDy<br>28.7 (20.8) CPZy | 0.8–5.1<br>10.4–41.3 |

IQR = interquartile range, CPZy = antipsychotic dose years in chlorpromazine equivalents, BZDy = benzodiazepine dose years in defined daily dose.

benzodiazepines only irregularly during the follow-up. The mean dose during the follow-up was 6.7 (SD 8.2) BZDy.

### 3.3. Association between cumulative antipsychotic dose during the follow-up and brain changes

Higher scan interval CPZy associated with increased lateral ventricle volumes ($b = 0.46$, $p = 0.012$) and decrease in volumes of total GM ($b = -0.38$, $p = 0.012$), cerebral GM ($b = -0.39$, $p = 0.012$), thalamus ($b = -0.34$, $p = 0.030$), hippocampus ($b = -0.34$, $p = 0.040$) and nucleus accumbens ($b = -0.38$, $p = 0.018$). After adjusting analyses with benzodiazepine BZDy and PANSS average score, only the finding regarding lateral ventricles remained statistically significant ($b = 0.50$, $p = 0.028$). Even when hospital days during the follow-up were added to the model, the association still remained ($b = 0.487$, $p = 0.035$).

On the brain areas where PANSS average score during the follow-up was statistically significantly associated with brain structure volume changes (total GM, cerebral GM and nucleus accumbens), the effect size of PANSS was roughly the same as the effect size of CPZy on those brain areas. The effect of onset age was also roughly the same as the effect of CPZy on the same areas. All results regarding all covariates and brain volumes are presented in Table 3. Tables 4.1 and 4.2 present the results of effects of CPZy and BZDy in adjusted analyses.

### 3.4. Association between cumulative benzodiazepine dose during the follow-up and brain changes

Higher scan interval benzodiazepine BZDy associated with increase in the volume of the lateral ventricles ($b = 0.35$, $p = 0.037$) and decrease in the following volumes: total brain ($b = -0.35$, $p = 0.037$), cerebrum ($b = -0.32$, $p = 0.048$), caudate nucleus ($b = -0.49$, $p = 0.002$), thalamus ($b = -0.36$, $p = 0.033$) and nucleus accumbens ($b = -0.40$, $p = 0.018$). After adjusting for CPZy and PANSS average score only the finding regarding the caudate nucleus remained statistically significant ($b = -0.42$, $p = 0.029$).

### 3.5. Post hoc analyses

In post hoc analyses, the mean volumes for lateral ventricle volume change was 11.9 in the high antipsychotic/high benzodiazepine group, 6.7 in high antipsychotic/low benzodiazepine group, 4.7 in low antipsychotic/high benzodiazepine group and 2.7 in low/low group. The mean volumes for caudate nucleus change were −0.33 in high/high group, −0.08 in high/low group, −0.11 in low/high group and 0.16 in low/low group. Analysis of variance documented a main effect of antipsychotic dose in the lateral ventricles ($F_{1,34} = 5.5$, $p = 0.025$), with no main effect of benzodiazepine dose ($F_{1,34} = 2.28$, $p = 0.14$) and no interaction ($F_{1,34} = 0.46$, $p = 0.5$). In the caudate, there was a main effect of benzodiazepines ($F_{1,34} = 4.83$, $p = 0.035$), a marginal main effect of antipsychotic dose ($F_{1,34} = 3.97$ $p = 0.054$) and no interaction ($F_{1,34} = 0.001$ $p = 0.971$).

In analyses of association between alcohol use disorder diagnosis

**Table 3**
Associations between medication variables and other covariates and change of brain volumes between the age of 34 years and 43 years in schizophrenia. Sex and ICV at the age of 34 years are covariates in all analyses. Statistically significant (p < 0 05) findings are in **bold**.

| Brain area | CPZy | BZDy | PANSS | Age of illness onset | Number of hospitalization days |
|---|---|---|---|---|---|
| Total Brain | b = −0.269<br>p = 0.088 | **b = −0.346**<br>**p = 0.037** | b = −0.088<br>p = 0.590 | b = 0.061<br>p = 0.713 | **b = −0.342**<br>**p = 0.027** |
| Total GM | **b = −0.380**<br>**p = 0.012** | b = −0.151<br>p = 0.367 | **b = −0.373**<br>**p = 0.013** | **b = 0.429**<br>**p = 0.005** | b = −0.181<br>p = 0.242 |
| Cerebrum | b = −0.261<br>p = 0.092 | **b = −0.324**<br>**p = 0.048** | b = −0.083<br>p = 0.607 | b = 0.046<br>p = 0.779 | **b = −0.307**<br>**p = 0.045** |
| Cerebrum GM | **b = −0.387**<br>**p = 0.012** | b = −0.152<br>p = 0.376 | **b = −0.370**<br>**p = 0.015** | **b = 0.414**<br>**p = 0.009** | b = −0.182<br>p = 0.250 |
| Lateral ventricles | **b = 0.458**<br>**p = 0.003** | **b = 0.355**<br>**p = 0.037** | b = 0.212<br>p = 0.211 | b = −0.301<br>p = 0.069 | b = 0.312<br>p = 0.050 |
| Caudate | b = −0.294<br>p = 0.062 | **b = −0.489**<br>**p = 0.002** | b = −0.250<br>p = 0.117 | b = 0.152<br>p = 0.357 | **b = −0.394**<br>**p = 0.012** |
| Putamen | b = −0.303<br>p = 0.074 | b = −0.266<br>p = 0.144 | b = −0.250<br>p = 0.154 | b = 0.283<br>p = 0.107 | **b = −0.343**<br>**p = 0.046** |
| Thalamus | **b = −0.344**<br>**p = 0.030** | **b = −0.360**<br>**p = 0.033** | b = −0.257<br>p = 0.121 | b = 0.197<br>p = 0.238 | **b = −0.384**<br>**p = 0.013** |
| Hippocampus | **b = −0.340**<br>**p = 0.040** | b = −0.184<br>p = 0.306 | b = −0.163<br>p = 0.337 | b = 0.140<br>p = 0.424 | **b = −0.566**<br>**p = 0.0003** |
| Accumbens | **b = −0.378**<br>**p = 0.018** | **b = −0.404**<br>**p = 0.018** | **b = −0.369**<br>**p = 0.023** | **b = 0.497**<br>**p = 0.002** | b = −0.312<br>p = 0.055 |

CPZy = antipsychotic dose years in chlorpromazine equivalents during follow-up, BZDy = benzodiazepine dose years in defined daily dose during follow-up, ICV = intracranial volume, GM = grey matter, b = standardized beta, PANSS = The average score of Positive and Negative Syndrome Scale (PANSS) total score at 34 years and 43 years.

**Table 4.1**
Associations between independent variables and brain structural change during the follow up, and statistically significant associations between antipsychotic dose years, benzodiazepine dose years, and PANSS average score and brain structural changes in the same model. ICV and sex as covariates in all analyses. Statistically significant (p < 0 05) findings are in **bold**.

| Brain area | CPZy | BZDy | PANSS | CPZy, BZDy and PANSS in the same model |
|---|---|---|---|---|
| Total Brain | b = -0.269<br>p = 0.088 | **b = -0.346**<br>**p = 0.037** | b = -0.088<br>p = 0.590 | BZDy<br>b = -0.233 p = 0.252 |
| Total GM | **b = -0.380**<br>**p = 0.012** | b = -0.151<br>p = 0.367 | **b = -0.373**<br>**p = 0.013** | CPZy<br>b = -0.240 p = 0.252 |
| Cerebrum | b = -0.261<br>p = 0.092 | **b = -0.324**<br>**p = 0.048** | b = -0.083<br>p = 0.607 | BZDy<br>b = -0.210 p = 0.296 |
| Cerebrum GM | **b = -0.387**<br>**p = 0.012** | b = -0.152<br>p = 0.376 | **b = -0.370**<br>**p = 0.015** | CPZy<br>b = -0.250 p = 0.242 |
| Lateral ventricles | **b = 0.458**<br>**p = 0.003** | **b = 0.355**<br>**p = 0.037** | b = 0.212<br>p = 0.211 | **CPZy**<br>**b = 0.502 p = 0.028**<br>BZDy<br>b = 0.125 p = 0.517 |
| Caudate | b = -0.294<br>p = 0.062 | **b = -0.489**<br>**p = 0.002** | b = -0.250<br>p = 0.117 | **BZDy**<br>**b = -0.422 p = 0.029** |
| Putamen | b = -0.303<br>p = 0.074 | b = -0.266<br>p = 0.144 | b = -0.250<br>p = 0.154 | n.s. |
| Thalamus | **b = -0.344**<br>**p = 0.030** | **b = -0.360**<br>**p = 0.033** | b = -0.257<br>p = 0.121 | CPZy<br>b = -0.185 p = 0.419<br>BZDy<br>b = -0.241 p = 0.233 |
| Hippocampus | **b = -0.340**<br>**p = 0.040** | b = -0.184<br>p = 0.306 | b = -0.163<br>p = 0.337 | CPZy<br>b = -0.332 p = 0.176 |
| Accumbens | **b = -0.378**<br>**p = 0.018** | **b = -0.404**<br>**p = 0.018** | **b = -0.369**<br>**p = 0.023** | CPZy<br>b = -0.352 p = 0.727<br>BZDy<br>b = -0.244 p = 0.270 |

CPZy = antipsychotic dose years in chlorpromazine equivalents during follow-up, BZDy = benzodiazepine dose years in defined daily dose during follow-up, ICV = intracranial volume, GM = grey matter, b = standardized beta, PANSS = The average score of Positive and Negative Syndrome Scale (PANSS) total score at 34 years and 43 years, n.s. = non-significant.

and brain structural change in schizophrenia there were no statistically significant results, see Supplement Table 5 for details.

## 4. Discussion

### 4.1. Main results

In this study we found that in subjects with schizophrenia, higher antipsychotic medication dose during the follow-up related to increase in lateral ventricular volume when taking into account illness severity measures and benzodiazepine dose. Higher benzodiazepine dose associated with caudate volume reduction after adjusting for average PANSS score and antipsychotic dose.

### 4.2. Antipsychotic use and brain volume change

In a partly overlapping NFBC1966 sample we have found that in schizophrenia, a higher amount of antipsychotic medication over the 9-year follow-up (between ages 34 and 43 years) predicted larger total brain volume loss (Veijola et al., 2014). Consistent with those results, here, using a different image analysis method, we noted associations between antipsychotic medication exposure and decrease in total grey

**Table 4.2**
Associations between antipsychotic dose and benzodiazepine dose and brain structural change during the follow-up and the statistically significant associations of antipsychotic dose, benzodiazepine dose, PANSS average score and hospitalization days during the follow-up in the same model. ICV and sex as covariates in all analyses. Statistically significant (p < 0 05) findings are in **bold**.

| Brain area | CPZy | BZDy | CPZy, BZDy, PANSS and hospitalization days in the same model |
|---|---|---|---|
| Total Brain | b =-0.269 | **b = -0.346** | BZDy |
| | p = 0.088 | **p = 0.037** | b = -0.091 p = 0.716 |
| Total GM | **b = -0.380** | b = -0.151 | CPZy |
| | **p = 0.012** | p = 0.367 | b = -0.229 p = 0.283 |
| Cerebrum | b = -0.261 | **b = -0.324** | BZDy |
| | p = 0.092 | **p = 0.048** | b = -0.095 p = 0.702 |
| Cerebrum GM | **b = -0.387** | b = -0.152 | CPZy |
| | **p = 0.012** | p = 0.376 | b = -0.239 p = 0.271 |
| Lateral ventricles | **b = 0.458** | **b = 0.355** | **CPZy** |
| | **p = 0.003** | **p = 0.037** | **b = 0.487 p = 0.035** |
| | | | BZDy |
| | | | b = 0.037 p = 0.879 |
| Caudate | b = -0.294 | **b = -0.489** | BZDy |
| | p = 0.062 | **p = 0.002** | b = -0.350 p = 0.141 |
| Putamen | b = -0.303 | b = -0.266 | n.s. |
| | p = 0.074 | p = 0.144 | |
| Thalamus | **b = -0.344** | **b = -0.360** | CPZy |
| | **p = 0.030** | **p = 0.033** | b = -0.153 p = 0.500 |
| | | | BZDy |
| | | | b= -0.052 p = 0.832 |
| Hippocampus | **b = -0.340** | b = -0.184 | CPZy |
| | **p = 0.040** | p = 0.306 | b = -0.245 p = 0.214 |
| | | | **hospitalization days b =-0.788** |
| | | | **p < 0.001** |
| Accumbens | **b = -0.378** | **b = -0.404** | CPZy |
| | **p = 0.018** | **p = 0.018** | b = -0.072 p = 0.754 |
| | | | BZDy |
| | | | b = -0.180 p = 0.468 |

CPZy = antipsychotic dose years in chlorpromazine equivalents during follow-up, BZDy = benzodiazepine dose years in defined daily dose during follow-up, ICV= intracranial volume, GM = grey matter, b= standardized beta, PANSS= The average score of Positive and Negative Syndrome Scale (PANSS) total score at 34 years and 43 years, n.s. = non-significant.

matter (with a marginal effect on total brain volume). These effects were attenuated when we controlled for potential confounding factors including benzodiazepine use, which we and others did not control for in previous studies. However, the association we observed here between antipsychotic medication exposure and lateral ventricular change was robust to controlling for illness severity and benzodiazepine use. In our previous studies in this sample using the FSL tool SIENA to examine movement over time (atrophy) at the brain edge, we noted an association between higher antipsychotic medication dose and lateral ventricular volume increase (Veijola et al., 2014), and periventricular brain volume reductions at the fourth ventricular edge (Guo et al., 2015). When viewing these studies using different methods together, it appears in our sample that there is a consistent association between antipsychotic medication exposure and ventricular volume change. Furthermore, we find that antipsychotic dose predominantly relates to increase in lateral ventricle volume independent of benzodiazepine dose. However, we recognize that not all other studies have noted similar effects (Ho et al., 2011; Saijo et al., 2001; Puri et al., 2001).

We have also studied cognition in this sample in relation to medication. Higher dose-years of antipsychotics associated with decline in verbal learning and memory between ages 34 and 43 years (Husa et al., 2014). High lifetime dose and antipsychotic polypharmacy associated also with poorer outcomes in schizophrenia at the age of 43 years (Moilanen et al., 2015). These results are consistent with the possibility that long-term antipsychotic medication has some adverse effects on the brain, although it remains possible that residual confounding may be responsible for these associations. For example, although we adjust for illness severity in our sample, we did not have information on severity of illness (e.g. symptoms) for the entire follow-up period. Patients with the most severe illness may be the ones who are prescribed the most medication by doctors attempting to regain symptom control, but it may be that a more severe disease process results, through unknown mechanisms unrelated to medication, in the most cognitive decline and the most progressive brain atrophy.

The potential antipsychotic effect on brain structures in schizophrenia was suggested in the 1970's by Marsden (Marsden, 1976) in response to the report on lateral ventricle increase in schizophrenia by Johnstone et al. (1976). Since then the issue has been raised again in the 2000's as the effects of second-generation antipsychotics on the brain started to be studied and compared with traditional first-generation antipsychotics (e.g. Crespo-Facorro et al., 2008; Lieberman et al., 2005; Mamah et al., 2012; Roiz-Santiáñez et al., 2012). Animal studies have examined different antipsychotic agents and treatments, and the results suggest that antipsychotics may have effects on brain structures even when illness related confounding factors present in human studies are excluded (Dorph-Petersen et al., 2005; Vernon et al., 2014, 2011).

The possible mechanism behind antipsychotic-related structural brain changes is not clear. In striatal areas antipsychotics may increase striatal metabolism as a consequence of increased firing rates induced by antipsychotic induced presynaptic D2 blockade, possibly leading to increased volumes (Buchsbaum et al., 1992). This has been associated especially to typical antipsychotic use, whereas some studies have found atypical antipsychotics to even reverse this effect after switching (Lang et al., 2004; Scheepers et al., 2001). However, a systematic review on antipsychotic monotherapy effects in basal ganglia reported that no studies found typical antipsychotics to induce basal ganglia volume increases, but atypical antipsychotics have been associated to both increases and decreases (Ebdrup et al., 2013). Wide-spread reductions in cortical volumes in antipsychotic exposed monkeys (Dorph-Petersen et al., 2005) compared to sham treatment were traced to result from lower astrocyte number in the antipsychotic treated groups (Konopaske et al., 2008). On the contrary, antipsychotic induced decrease in volume and thickness of anterior cingulate cortex in rats was not associated to decrease in astrocyte number but instead to decrease in neuropil (Vernon et al., 2014). Antipsychotics may also induce autophagy, a process related to neurodegeneration and cell death, which may contribute to volumetric changes (Shin et al., 2012).

### 4.3. Benzodiazepine use and brain volume change

Though the association of antipsychotic medication on structural changes in the brain has gained considerable attention in the previous years, the effects of benzodiazepines have not been taken into account. In studies with over 2 year follow-ups looking at associations between antipsychotics and brain MRI findings in schizophrenia only one used benzodiazepine use as an exclusion criteria (Molina et al., 2005), 5 reported in their methods that subjects used also benzodiazepines (Takahashi et al., 2012, 2011a, 2011b, 2010, 2009) and only one study briefly discussed the potential confounding effect of benzodiazepine use and need for further research on how benzodiazepines may affect brain structures (Takahashi et al., 2010).

In our study, in the post hoc analysis regarding caudate volume change, among those with low doses of both antipsychotics and benzodiazepines the volume increased, whereas the decrease was largest among those using both on high doses and the second largest when the antipsychotic dose was low but the benzodiazepine dose was high.

Analysis of variance confirmed a significant main effect of benzodiazepine dose, with only a marginal effect of antipsychotic dose, and no evidence of interaction. This suggests that the change in caudate nucleus volume relates to benzodiazepine exposure rather than being driven by an association with antipsychotic medication or any interacting effect of these two medications. In summary, the effect of antipsychotics and benzodiazepines may be more additive than multiplicative.

The results of earlier CT studies on benzodiazepine effects on brain structures are inconsistent, though the topic has not been studied extensively. The most recent studies on benzodiazepine effects on brain structures detected by CT concluded that long-term benzodiazepine use does not result in brain abnormalities (Busto et al., 2000; Lader et al., 1984; Moodley et al., 1993; Perera et al., 1987). However, two studies have found that benzodiazepines associate to increased ventricle-to-brain ratio (Schmauss and Krieg, 1987; Uhde and Kellner, 1987) with one even suggesting a dose-dependent effect (Schmauss and Krieg, 1987).

Long-term benzodiazepine use has been linked to cognitive dysfunction, and even after withdrawal patients may not return to the level of cognition of matched controls without benzodiazepine use (Barker et al., 2004b). A study of schizophrenia cases treated with second generation antipsychotics found that after tapering off benzodiazepines the cognitive performance improved significantly and there was also improvement in quality of life and decrease in PANSS total scores (Kitajima et al., 2012).

There is no current knowledge on the exact mechanism how benzodiazepines could affect brain structures in humans. However, animal studies have found that brain-derived neurotrophic factor (BDNF) levels decreased after acute, but not repeated administration of the benzodiazepine triazolam and closely related drug zolpidem in the mouse hippocampus (Licata et al., 2013b); that mice treated with benzodiazepines showed decrease in density of the spines of pyramidal neurons (Curto et al., 2016) and diazepam reduced the level of transcripts involved in synaptic functions and neural plasticity (Huopaniemi et al., 2004). BDNF regulates neuronal connectivity and synaptic efficacy (Lu, 1999) and plays a key role in neural plasticity (Duman, 2004). Zolpidem has also found to alter the function of resting-state networks in healthy individuals (Licata et al., 2013a), and functional aberration often leads to structural changes as well (Keck et al., 2011). Since benzodiazepine use has been associated with decline in cognition and decreased structural plasticity in mice, there is a need for understanding the mechanisms behind benzodiazepine effects on the brain at cellular and macroscopic levels.

Knowing the potential effects and adverse effects benzodiazepines may have on brain structure and functioning is essential in schizophrenia, because the prevalence of benzodiazepine use varies from 15% to even 91% (Mundt et al., 2012; Vares et al., 2011; Waterreus et al., 2012). In NFBC1966, 42% of individuals with schizophrenia used benzodiazepines at the age of 43 (Nykänen et al., 2016), and in our study, 95% of patients had used benzodiazepines prior to study commencement, with 79% using them in the inter-scan interval. Altogether, in our sample, the use of benzodiazepines was extremely high, and this is not supported by recent results on their possible harmful effects regarding e.g. mortality in schizophrenia (Fontanella et al., 2016) and cognition (Baandrup et al., 2017). In addition, benzodiazepines are commonly used in the general population: approximately 3% use benzodiazepines over 6 months and in some populations the number is even higher (Kurko et al., 2015). The fact that these medications are so widely used underlines the importance of studying their long-term effects carefully.

### 4.4. Methodological discussion

This study partly demonstrates the importance of using adequate covariates when studying variables that are sensitive to confounding factors. Previous studies have not taken illness severity and potential confounding medication into account comprehensively (Huhtaniska et al., 2017). Taking illness related factors into account in this study was also challenging, since the used variables correlated with each other (see Supplement Table 6). When we examined the collinearity between the variables used in our analyses, the degrees of multicollinearity was moderate and at an acceptable level to conduct the analyses (see Supplement Tables 7 and 8 for details).

Imaging studies are often sensitive to confounding effects due to various reasons. To exclude natural variation in brain volumes between two time point images, the protocol before each scan should be as strictly the same as possible, for example the diet and fluid intake should be comparable. The scanner should be the same, it should not be updated and phantoms should be imaged frequently for maximal quality. Issues rising from these factors potentially confound the results of imaging studies and though they are well-known, they are hard to rule out when conducting longitudinal studies.

### 4.5. Strengths and limitations

A major strength of this study is the use of comprehensive, thoroughly collected medication data. To our knowledge, there are no other MRI studies with data on long-term longitudinal use of both antipsychotics and benzodiazepines. Our data has been collected using several sources: by interviewing the person themselves and by scrutinizing all available medical records and collecting all available information on prescribed doses and duration of treatments.

Another strength is the rare naturalistic setting that is tailor-made for studying long-term associations, effects and adverse effects of medications (Wang et al., 2011). For example the observed wide range in the used doses of both studied medications reflects the clinical reality. Naturalistic settings may provide novel information and perspective in contrast to clinical studies that are often made with determined objectives and in more strictly selected study populations.

A limitation in our study is the sample size. Though there were 101 identified schizophrenia cases in the NFBC1966 in the beginning of this study, only 73 of them participated at baseline and 45 at follow-up. Possibly partly because of active home-recruitment in our study, the participants did not differ from the non-participants in terms of age, sex or educational level (Veijola et al., 2014). Still, we cannot be certain this sample represents the whole schizophrenia population extensively in all measured domains.

The small sample size limits the statistical power to find associations, and due to several analyses performed some associations may be due to chance. We did not correct for multiple comparisons when analyzing different brain areas, since the size of brain structures are related to each other and a conservative correction method (e.g. Bonferroni) would probably over-correct the results. There were also some potential confounding factors that we were unable to take into account in our analyses, such as other medication use, dietary profile or physical activity during the follow-up. We tested whether alcohol use disorder affected the results, and found no evidence that it did, but we could not control for alcohol use as a continuous variable. In addition, we were unable to study or control for the role of non-pharmacological therapies used, since we do not have any data on possible psychosocial interventions. One potential issue is using PANSS summary score as a covariate in the analyses, since it is a sum based on original ordinal scale items. Despite this, PANSS summary scores are commonly used in psychiatric studies and analyses and therefore also used in this study as a measure of illness severity. Given these facts, the results of this study need to be interpreted cautiously and they need to be replicated, especially regarding the findings on benzodiazepines.

Another limitation is the uncertainty of how the scanner update affects our measures of brain volumes. However, we tried to overcome the possible interference by using test-retest measures. In any case, we emphasize that the results of this study are only observed differences between the MRI measures at two different time points and we do not conclude a causal effect.

### 4.6. Conclusions

Higher cumulative antipsychotic dose associates to ventricular enlargement in schizophrenia even after controlling for benzodiazepine use and illness related factors. Nevertheless, we cannot be sure if antipsychotics themselves cause the ventricular enlargement found in this study as the use of antipsychotics may be a marker for a factor we are unable to identify, which contributes to ventricular enlargement.

This study assessed the association between benzodiazepine use and structural brain changes for the first time in schizophrenia, and suggested an association with change in caudate volume. Our results suggest that in the future, studies should focus also on benzodiazepine effects on the brain and studies on antipsychotic effects should take benzodiazepine use into account as a potential confounder.

There is a need for understanding the mechanisms behind antipsychotic and benzodiazepine related structural and functional changes in the brain. Further studies should also focus on how medication related structural alterations correspond to cognition and functioning.

## Financial support

This study was supported by the University of Oulu Scholarship Foundation, the Jalmari and Rauha Ahokas foundation, the Orion Research Foundation sr, the Scholarship Fund of the University of Oulu – Tyyni Tani Found, the Foundation for Psychiatric Research, the Sigrid Jusélius Foundation, the Academy of Finland (#132071, #268336 and #278286), the Brain & Behavior Research Foundation, Northern Finland Health Care Support Foundation, the Universidad Carlos III de Madrid, the European Union's Seventh Framework Programme for Research, Technological Development and Demonstration under Grant agreement no. 600371, el Ministerio de Economía y Competitividad (COFUND2013-40258), el Ministerio de Educación, cultura y Deporte (CEI-15-17) and Banco Santander.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.05.009.

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